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Comparative oncology: what dogs and other species can teach us about humans with cancer

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Over 1.66 million humans (approx. 500/100 000 population rate) and over 4.2 million dogs (approx. 5300/100 000 population rate) are diagnosed with cancer annually in the USA. The interdisciplinary field of comparative oncology offers a unique and strong opportunity to learn more about universal cancer risk and development through epidemiology, genetic and genomic investigations. Working across species, researchers from human and veterinary medicine can combine scientific findings to understand more quickly the origins of cancer and translate these findings to novel therapies to benefit both human and animals. This review begins with the genetic origins of canines and their advantage in cancer research. We next focus on recent findings in comparative oncology related to inherited, or genetic, risk for tumour development. We then detail the somatic, or genomic, changes within tumours and the similarities between species. The shared cancers between humans and dogs that we discuss include sarcoma (osteosarcoma, soft tissue sarcoma, histiocytic sarcoma, hemangiosarcoma), haematological malignancies (lymphoma, leukaemia), bladder cancer, intracranial neoplasms (meningioma, glioma) and melanoma. Tumour risk in other animal species is also briefly discussed. As the field of genomics advances, we predict that comparative oncology will continue to benefit both humans and the animals that live among us.

1. Introduction

Comparative oncology is a quickly expanding field that examines both cancer risk and tumour development across species. Characterized by interdisciplinary collaboration, its goal is advancement of both human and animal health. Nowhere has this been more evident than in the investigation and comparison of canine and human tumours. The study of naturally occurring cancers in the domestic dog provides a suitable model for advancement of the understanding, diagnosis and management of cancer in humans [1–4]. There are over 70 million pet dogs in the USA, residing in over 40 million households [5,6]. With over 100 million vet visits each year in the USA, our dogs provide a powerful resource for closely monitored health data. Canine cancers occur spontaneously, and have similar clinical presentation and pathophysiology to equivalent human cancers. As such, they closely parallel the natural progression of human cancer to a greater extent than is observed in induced cancer animal models [7–9]; genomic analysis of canine tumours has revealed shared features between both species, providing fresh insight into the genetic basis of tumour development [10–12]. Additionally, society's practice of dog breeding has unwittingly created a high-risk model for breed-specific disease due to consanguinity and inbreeding [13,14]. The restricted genetic variation in many purebred dog breeds allows for easier identification of the genetic basis of disease, including cancers, and the shorter lifespan of dogs facilitates timely and efficient evaluation of new approaches to cancer diagnosis, treatment and prevention. This review will discuss the domestic dog as a model for comparative

oncology, with a focus on both inherited risk and tumour genomics, along with a brief assessment of other species relevant to the field of study.

(a) On the origin of dogs (and their cancer risk)

While there are probably over 400 breeds of dog recognized worldwide, the number of breeds recognized by the dog fancy in different countries varies. For example, in the USA the American Kennel Club (AKC) now recognizes 184 breeds of dog (including 21 varieties) and the United Kennel Club (UKC) recognizes over 300 breeds. The characteristics of each dog of a specific breed have been refined and maintained to meet the stringent breed standards and be considered a contender for selection as a champion.

Over 15 000 years ago, man's relationship with the dog was quite different, being one in which dogs were selected primarily for their function. Dogs helped humans to survive, using their fast pace to aid in hunting of animals and their strength and boldness to serve as protectors. Over the course of subsequent millennia, the relationship between man and dog continued to be one of co-dependency. Around the time of the industrial revolution, we started to breed dogs as much for their form as their function, in an industrializing society. In just the past few hundred years, intensive selection and breeding of dogs for key desirable traits resulted in the development of what we regard today as the major characteristics of the breed. When considered as a species, the level of genetic variation sampled across all dog breeds today is perhaps as extensive as for human populations [15]. In individual pure breeds, however, the level of genetic diversity is now variably restricted [16]. The process of breed formation over just the past 2–3 centuries has been estimated to have resulted in sevenfold greater reduction in genetic diversity than did the thousands of years of early domestication [17]. This is compounded further by the use of popular sires and gene pool decline during the twentieth century. Since many of the key phenotypes are characteristics of the particular breed, their presence in the breed had been positively selected, resulting in high frequency of the genes that cause these specific phenotypes. With such intense selection, it is perhaps not surprising that there are now over several hundred inherited diseases recognized in dogs. While some diseases have simple inheritance patterns, others, including cancers, are likely to be more complex. The genetic background of some purebred dogs may predispose the breed to a higher risk for specific cancers, or cancers in general. It is this increased risk of cancer in purebred dogs that may be leveraged to accelerate the process of cancer gene discovery from a comparative perspective.

The histological and clinical presentation of numerous canine cancers closely parallels that of the corresponding cancers in humans. The extended lifespan of the dog, combined with the shared environment and development of spontaneous cancers, places the dog in a unique position to better reflect cancer development and progression than traditional rodent models. As is the case for human and rodent models, the advancement of genomic technologies and the development of canine custom reagents and resources have facilitated studies of both somatic and inherited genomic variation in the domestic dog. As discussed in §2, canine cancers share evolutionarily conserved genomic changes that are found in their human counterparts. Man's best friend is already providing scientists

with an opportunity to generate data beneficial to both species [3,4,10,11,18,19].

2. Germline and cancer risk

Several purebreds of dog are known to have a high incidence and elevated risk of specific cancer subtypes, sometimes even more than one subtype. The high degree of expectation has led veterinarians and pathologists to associate specific cancers with certain breeds of dogs (table 1). Such breed-specific risk reflects the underlying genetics of the different breeds. The patterns of specific cancers found within dog breeds is very reminiscent of the human cancer predisposition syndromes, whereby inherited genetic mutations in humans lead to very specific cancer risks in related children and families [21–25]. In humans, knowledge of specific cancer risk leads to designated early cancer screening approaches to decrease morbidity and mortality [24–29]. High-risk breeds of dog can be thought of as if they carry a hereditary cancer syndrome, although breed-specific screening in asymptomatic dogs has not yet become standard of care. Interestingly, several of the human cancer predisposition genes have been found in the constitutional (germline) DNA of dogs with cancer; this includes *BRCA1/BRCA2* germline mutations in dogs [30,31] which leads to hereditary breast and ovarian cancer syndrome in humans and *TP53* germline mutations in dogs [32] which lead to Li–Fraumeni syndrome in humans with multiple different cancers.

In addition to known deleterious mutations, more common single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) (or combination of SNPs and CNVs) have been associated with disease risk in specific dog breeds. The approach of using genome-wide association studies (GWAS) in humans to identify disease-risk alleles has been relatively successful, with an explosion in published GWAS data over the past decade [33,34], although admittedly, revealing varying levels of clinically significant disease risk [35,36]. In dogs, the rewards of GWAS can be more readily realized owing to the genetic homogeneity readily found within dog breeds [15,37]. Indeed, this has been the case for several recent GWAS findings in canine cancer.

One of the first cancer GWAS to evaluate a canine cancer explored the risk of histiocytic sarcoma (HS) in the Bernese mountain dog (BMD) [38]. This exceedingly rare sarcoma in humans occurs frequently in a few breeds of dog, including BMD, flat-coated retriever, Rottweiler and golden retriever. The lifetime risk of developing a HS in BMDs is 15–25% [38,39]. The authors performed the first GWAS in 111 BMD cases and 117 BMD controls from North America, as well as a second GWAS in 125 BMD cases and 117 BMD controls from Europe. Independent and combined analyses identified a significant risk allele on dog chromosome (CFA) 11 (North American BMD: $P_{raw} = 1.41 \times 10^{-9}$, European BMD: $P_{raw} = 1.50 \times 10^{-6}$, combined BMD: $P_{raw} = 1.11–10^{-13}$). Follow-up fine mapping and targeted sequencing revealed a shared haplotype in 96% of affected BMDs that included *MTAP* and part of *CDKN2A* (two very well-described cancer genes in humans). The exact mechanism leading to HS is still under investigation. Humans with germline *MTAP* mutations have been reported and these individuals develop diaphyseal medullary stenosis with malignant fibrous histiocytoma (a soft tissue sarcoma) [40]; humans with germline *CDKN2A*

Table 1. Cancers associated with specific dog breeds (data from authors and [13,20]).

cancer subtype	dog breed
lymphoma (unspecified)	Old English sheepdog, boxer, pointer, golden retriever, Rottweiler, St Bernard, Scottish terrier, bulldog
— B-cell lymphoma	— Irish wolfhound, Siberian husky, shih tzu, Airedale terrier, Cavalier King Charles spaniel, Yorkshire terrier
— T-cell lymphoma	— boxer, cocker spaniel, basset hound
osteosarcoma	large and giant breeds, such as Irish wolfhound, Scottish deerhound, Great Dane, BMD, mastiff, St Bernard, Irish setter, golden retriever, Rottweiler, Dobermann pinscher, greyhound
soft tissue tumours	larger dogs, such as boxer, BMD, Airedale terrier, Great Dane, St Bernard, basset hound, golden retriever—all with twice as many as the general canine population
hemangiosarcoma	German shepherd, BMD, golden retriever, flat-coated retriever, Portuguese water dog, Labrador retriever, boxer, Skye terrier, Australian shepherd
hs/malignant histiocytosis	BMD, flat-coated retriever, Rottweiler, golden retriever
mast cell tumours	boxer, pug, Labrador retriever, golden retriever, vizsla
meningiomas	mesocephalic (medium) and dolichocephalic (long)-nosed breeds, e.g. Labrador, golden retriever, collies
gliomas (including glioblastoma multiforme)	brachiochephalic (short-nosed) breeds, including boxers, bulldogs and terriers
testicular seminoma	Norwegian elkhound
nasal cavity carcinoma	golden retriever, beagle, Boston terrier, rough collie, Belgian shepherd
UC	Scottish terrier, beagle, West Highland white terrier, Shetland sheepdog, American Eskimo dog, standard schnauzer
lower urinary tract carcinoma	Airedale terrier, beagle
squamous cell carcinoma (digit)	STPO, giant schnauzer
melanoma	
— oral melanoma	— poodles
— cutaneous melanoma	— schnauzers, beauce shepherds

mutations develop melanoma and pancreatic cancer [41,42]. Clearly, the story of HS risk in dogs is only just beginning, and when combined with tumour genomics (see §3), there is still much to be learned to the benefit of both dogs and their human owners.

The same group also investigated the very specific increased risk for squamous cell carcinoma of the digit (SCCD) found to be especially prevalent in standard poodles (STPOs) [43]. This aggressive cancer causes lytic bone lesions of a focal nature, but interestingly, SCCD almost always occurs in dark-coated STPOs and rarely in their light-coated counterparts. The authors performed a GWAS, comparing 31 SCCD cases in STPOs to 34 unrelated black STPO controls. The GWAS identified a statistically significant peak SNP localized to CFA 15 ($P_{raw} = 1.60 \times 10^{-7}$). Further genotype mapping discovered a minimal region of less than 30 kilobases (kb) that contained the KIT Ligand (KITLG) gene locus with a CNV with at least four copies due to a tandem repeat. Since both the light-coloured and dark-coloured STPOs carry this KITLG tandem repeat, a subsequent GWAS compared light and dark STPOs ($N = 24$ versus 24) and identified the MC1R locus to be the only difference between the groups ($p = 2.52 \times 10^{-15}$). The study authors concluded that mutations found with MC1R may actually be cancer protective for light-coloured STPOs, and that MC1R may be interacting with KITLG CNVs as a genomic modifier. In humans, KITLG is not associated with cancer risk, although rare germline KIT mutations have been associated with familial gastrointestinal stromal tumours (GIST), a type of gastrointestinal sarcoma [44]. Interestingly, there is precedent for the role of MC1R as a modifier of disease, as germline MC1R variants in humans affect pigmentation [45,46] and seemingly function as genomic modifiers for several human diseases [47–51], in one study conferring risk for BRAF-mutant melanoma [52].

A third canine cancer GWAS has been performed to identify risk of osteosarcoma. Using a study cohort comprising 492 dogs as 261 cases and 231 controls across three breeds (greyhounds, Rottweilers and Irish wolfhounds), the GWAS identified 33 different inherited risk loci that could explain 55–85% of the phenotype variance in each breed [53]. The strongest association within the greyhounds was within a 150 kb segment upstream from CDKN2A/B, one of the most highly rearranged genes detected in canine osteosarcoma tumour cells. This study revealed a polygenic series of germline-risk factors that collectively highlighted specific pathways as drivers of disease. Consistent with the biology of the tumour, the candidate regions were enriched for genes in bone differentiation and growth pathways. A GWAS in human osteosarcoma also was recently published by Savage et al. [54], but with different findings than in the dog; they analysed 941 individuals with osteosarcoma and 3291 cancer-free adult controls of European ancestry and found a very high statistical association with disease risk in GRM4 located at 6p21.3 ($p = 8.1 \times 10^{-9}$) and two SNPs in the gene desert at 2p25.2 ($p = 1.0 \times 10^{-8}$ and 2.9×10^{-7}). As Machiela & Chanock [37] discuss, although GRM4, which is involved in intracellular signalling and inhibition

of the cyclic AMP signalling cascade, was not found to be associated itself with canine osteosarcoma, *GRIK4*, another glutamate receptor, was significantly associated with osteosarcoma risk in greyhounds; also, the SNPs close to *GRM4* were fixed in Rottweilers with osteosarcoma [53]. This comparative approach may provide novel insight and validation of signalling pathways associated with osteosarcoma risk in both humans and dogs. More comparison work is currently underway.

The most recent canine cancer GWAS explored the genetic risk for haematologic malignancy in the dog, specifically B-cell lymphoma and haemangiosarcoma in golden retrievers [55]. These cancers occur at high rates in this breed (B-cell lymphoma 6% and haemangiosarcoma 20%), and the investigators looked at 148 haemangiosarcoma cases versus 41 B-cell lymphoma cases versus 172 cancer-free controls. When the results from each GWAS were combined, two associated loci were identified on CFA 5 and contributed nearly 20% of the risk for haemangiosarcoma and B-cell lymphoma (4.6×10^{-7} and 2.7×10^{-6}, respectively). Whole genome sequencing (WGS) of nine cases and controls discovered risk haplotypes without coding changes. The authors investigated gene expression in B-cell lymphoma tumours and concluded that these germline-risk alleles affect T-cell regulatory pathways and immune-mediated responses. Based on their canine GWAS findings, the authors conclude that the immune system and malignant cells may interact in tumour risk and development [55], a hypothesis that now can be explored in other haematologic malignancy models and even primary tumours in humans. In support of this concept, recent human GWAS in diffuse large B-cell lymphoma [56], follicular lymphoma [57] and marginal zone lymphoma [58] have all demonstrated a role for immune recognition and immune function, with lymphoma risk strongly linked to HLA and other regions [56–58].

A striking and recurrent theme in the analysis of canine cancer GWAS data compared to comparable human GWAS is the ability to analyse a much lower number of canine cases and controls to identify risk factors compared to human studies of identical cancers. The actual number of cases and controls depends on a variety of factors, but, in general, it is evident that the restricted level of genetic heterogeneity in purebred dogs provides opportunities for an efficient means to identify risk loci for cancers that may be of comparative value to human studies.

3. Somatic and tumour genomics

Identification of risk for developing cancer is a key factor in health management of the individual and the population. Once constitutional changes to the canine genome have been determined, these data offer a powerful approach to screen and stratify populations by risk. Within purebred lines, knowledge of risk will play a key role in selecting more informed breeding programmes designed to reduce carefully the frequency of deleterious alleles in the population. The inherited risk of a cancer may not be directly related to the genome dysregulation associated with initiation and/or propagation of tumour cells, and so be of little to no value in making decisions about patient care once a cancer develops. Genome-wide assessment of changes at the somatic level is therefore another key area of active research in comparative oncology. Identification of recurrent genome changes in

cancer cells is a key approach to identifying potential targets for therapeutic intervention. The introduction of molecular genetic tools has revolutionized the way we are able to interrogate cancer cells to identify specific changes in gene dosage, organization and regulation. Numerical and structural changes to the genome have been identified in over 65 000 cases of human cancer, representing over 70 different types of cancer (see http://cgap.nci.nih.gov/Chromosomes/Mitelman). Many of these recurrent chromosome aberrations initially were associated with histopathological or immunological subgroups, leading to their use as diagnostic signatures. More recently the cytogenetic status of tumour cells has been demonstrated to be of established clinical value for prognosis, guiding therapy and assessing remission for a range of cancers, including ovarian cancer [59], colorectal carcinoma [60,61], gliomas [62], melanoma [63,64] and breast carcinoma [65]. From the perspective of comparative oncology, we may consider all animals to be differentially organized collections of the same collection of ancestrally related genes. As such, assessment of changes to genome architecture in canine cancers has been an active area of research, aimed at identifying regions of genome aberration shared between canine and human cancers, suggestive of a conversed mechanism of pathogenesis.

(a) Sarcomas

In the USA, it is estimated that approximately 500 new cases of cancer are diagnosed per 100 000 of the population each year (http://seer.cancer.gov), whereas in dogs the estimate is approximately 5300 cancer diagnoses/100 000 population (AVMA, 2011). These figures are striking in that they indicate that $2.5\times$ the number of cancers are diagnosed in pet dogs each year and that this represents an incidence of over $10\times$ that of the human population with which they live. Approximately 50% of all human cancer-related deaths in the USA in 2014 were the result of just four types of cancer, all of which were carcinomas; pulmonary, prostate and colon carcinoma in males, and breast, pulmonary and colon carcinoma in females (figure 1). While accurate numbers of cancers in pet dogs are not known, extrapolation from extensive academic records suggests that almost 60% of the estimated 1 500 000 diagnosed malignant cancers in dogs in the USA each year are represented by a combination of sarcomas and carcinomas (figure 1). The apparent lower numbers of pulmonary and colon carcinoma in pet dogs may in part be due to the human-specific influences (diet and smoking) affecting rates of these prevalent cancers, both of which are associated with factors not necessarily shared with pet dogs. Considering some of the most prevalent cancers in human, the corresponding canine cancers are highly evident also (figure 2) indicating the potential for the role of the dog as an appropriate biological model system.

(i) Osteosarcoma

Osteosarcoma is the most common human bone tumour in adolescents and young adults. This aggressive bone tumour has been associated with germline *TP53* mutations (Li–Fraumeni syndrome), among other hereditary cancer syndromes [66]. With the introduction of combination chemotherapy and multimodal approaches, the cure for human osteosarcoma has risen to nearly 70%, although it still remains at less than 20% for relapsed or recurrent disease [67,68]. Although relatively rare in humans, with up to 75 000 cases of canine osteosarcoma
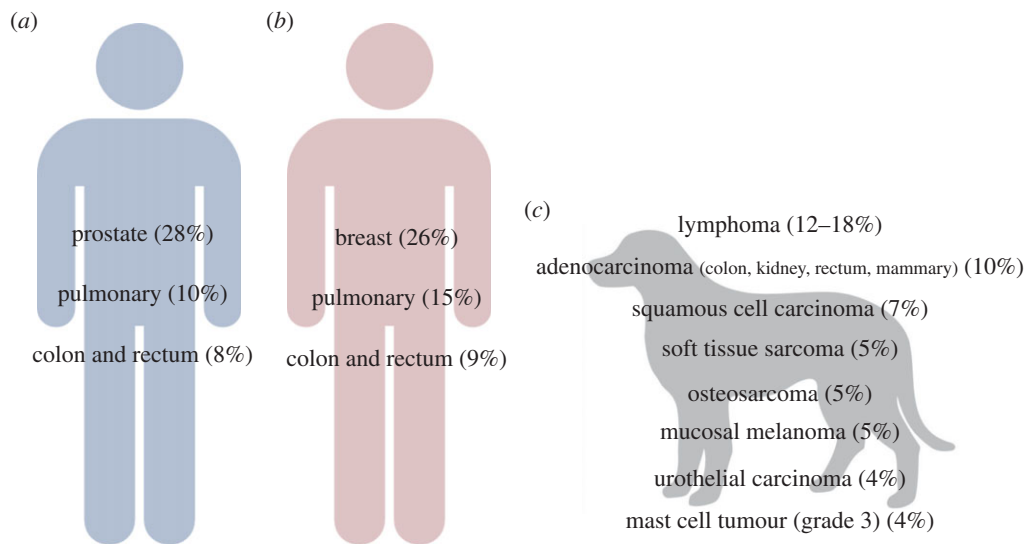
Figure 1. Frequency of cancer-related deaths in human and dog. Approximately 50% of all human cancer deaths in the USA each year are a consequence of four cancers, two of which are common to males (*a*) and females (*b*) (human data from (http://www.cancer.org)). (*c*) The estimated annual frequencies of death-related malignant cancers in pet dogs in the USA are shown (extrapolated canine data from US academic accessions). (Online version in colour.)
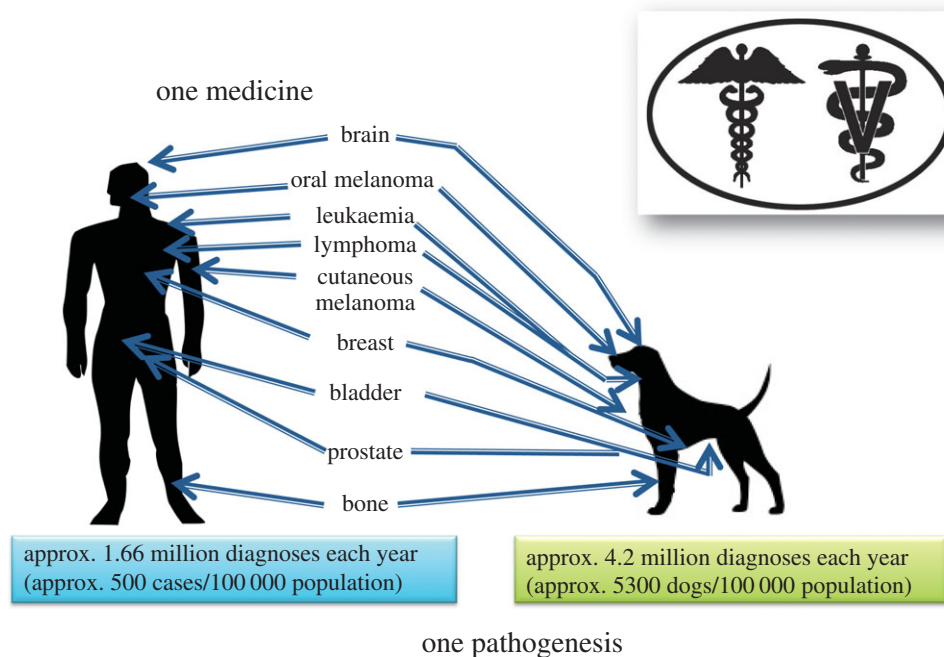

Figure 2. The remarkable similarity in cancers shared by human and dog. The cancers shown are found in both human and canine populations, and several ongoing studies are highlighting the similarities at the genomic level. The incidence of cancers in both species is shown, highlighting the more than $2.5\times$ number of cancers diagnoses in pet doges each year. Comparative oncology is a growing trans-disciplinary field that harnesses these data, adding evidence to support a shared pathogenesis. (Online version in colour.)

diagnoses each year in the USA, the rate is as high as $75\times$ that of humans. Breeds considered at high risk of developing canine osteosarcoma tend to be some of larger and giant breeds, including the Rottweiler, Great Pyrenees, mastiff, Dobermann pinscher, Irish wolfhound, Scottish deerhound. Given its frequency in canines, the dog model of naturally occurring osteosarcoma has offered an unparalleled opportunity to understand the genomic origins of osteosarcoma, to learn about the role of metastasis in disease and to pilot new investigational drugs in trials that would otherwise take too long to accrue in humans [12,69]. Several years ago, Scott *et al.* [70] took advantage of the genetic homogeneity in dogs to identify molecular subtypes of osteosarcoma based on genome-wide

gene expression profiling in a cohort of high-risk breeds of dogs with osteosarcoma ($N = 79$). In this study, the authors were able to divide samples into two distinct subgroups based on gene expression that also correlated with overall survival. Similar to human osteosarcoma, the two canine groups involved 'G2/M transition and DNA damage checkpoint' and 'microenvironment-interaction'. As the authors conclude, the genomic findings in canine osteosarcoma are of benefit for both dogs and humans, and further investigation 'may enhance prognosis and prediction, and identify relevant therapeutic targets' [70].

In a parallel study, Angstadt *et al.* [71] used high-resolution oligonucleotide aCGH to interrogate copy number alterations (CNAs) in canine osteosarcoma ($N = 23$, various

breeds) and compared the data directly with cases of human osteosarcoma ($N = 15$). The authors demonstrated that even though osteosarcoma is a cancer with enormous genomic instability, the identification of common regions of conserved genomic alterations between species provides a means to narrow the search for genomic drivers versus passengers. This study identified shared regions of CNAs that were less than 500 kb in size between dog and humans and then interrogated those regions for orthologous osteosarcoma-associated genes. Genes with known association in osteosarcoma were revealed (*CDC5L, MYC, RUNX2* and *CDKN2A*/*CDKN2B*) as well as new genes that had not been described previously in osteosarcoma (*ADAM15, CTC1, MEN1, CDK7*, along with several more genes) [71].

Primarily a cancer of children and young adults, osteosarcoma is rare, with fewer than 1000 cases each year diagnosed in the USA. As such, a major challenge to the progress of human osteosarcoma clinical trials is low patient accrual. The high number of canine osteosarcomas diagnosed each year, combined with the remarkable motivation of dog owners to enroll their pets in clinical trials offers a tremendous opportunity to advance studies for this cancer. The net result is that both biological and clinical studies can be performed with pet dogs that would otherwise take an inordinately long period of time to accomplish in humans. In the study of osteosarcoma progression and metastasis, key advances have been made by the Comparative Oncology Program at the National Institutes of Health (NIH) through the study of dogs, including the recognition of the role of ezrin [12,72–75]. Furthermore, early clinical trials are now ongoing in dogs in conjunction with the Children's Oncology Group in North America, an approach that will quickly ascertain the effectiveness of osteosarcoma therapy, owing primarily to the much larger number of dogs with osteosarcoma compared with humans [12,72,76–78]. With time and additional canine trials, researchers believe the success of this approach will become readily apparent.

(ii) Soft tissue sarcoma

In 2013, Caserto published a comprehensive review of canine and human rhabdomyosarcoma (RMS) with an emphasis on comparing the classification and pathogenesis of this soft tissue sarcoma [79]. Not surprisingly, there were numerous similarities between RMS in both species, including their histological classification. Caserto described the ability to diagnose RMS in dogs using immunohistochemical (IHC) stains for desmin, α-actins, myogenin and MyoD1, in addition to electron microscopic identification of sarcomeric structures [79]. More recently, Milovancev *et al.* [80] have described non-RMS soft tissue sarcomas in dogs and their comparison to human non-RMS tumours. In this study, veterinary and human pathologists interpreted 32 clinically archived, canine soft tissue sarcomas. There was general agreement on the diagnoses and their similarities to human tumours, including low-grade spindle cell sarcomas ($N = 13/32$), undifferentiated sarcoma ($N = 32$), liposarcoma with atypical desmin-positive epithelioid cells ($N = 5/32$), spindle cell sarcoma with myxoid features ($N = 5/32$) and myxofibrosarcoma ($N = 2/32$). The comparative genomics of soft tissue sarcomas, both RMS and non-RMS, is a field that will continue to grow as technology advances and more of these rare tumours are collected in canines.

(iii) Histiocytic sarcoma

Canine HS is a very aggressive and rapidly fatal sarcoma of dendritic cell origin with a tendency to metastasize to the spleen and lungs. This cancer is very commonly reported in just two less abundant breeds of dog, the BMD and flat-coated retriever, and also in large numbers of three of the most popular breeds, including the Rottweiler, golden retriever and Labrador retriever [81–83]. The BMD is extraordinarily susceptible to this sarcoma, with as many as 25% of the breed diagnosed at a young age [38,39]. In humans, the equivalent of HS is not quite so clear; human HS is a very rare tumour, presents in lymph nodes, skin, and the gastrointestinal tract, often will be misdiagnosed as non-Hodgkin lymphoma (NHL), and is considered a diagnosis of exclusion [84,85]. As is the case with osteosarcoma, comparative oncology of HS offers a unique opportunity to leverage data from the canine disease to learn more about a poorly understood human cancer [86].

Hedan *et al.* [86] used molecular cytogenetic profiling with aCGH in spontaneously occurring HS from BMDs and flat-coated retrievers ($N = 104$ total) [86]. The data indicated a high level of genome disruption and instability, and the investigators identified that many of the highly recurrent CNAs were shared between both breeds, suggesting a common underlying pathogenesis. Specially, recurrent deletions were detected in commonly described human tumour suppressor genes, including *CDKN2A/B*, *RB1* and *PTEN* [86]. Interestingly, the GWAS of canine HS in BMDs (see above) localized a possible HS-risk allele also to *CDKN2A* (in addition to *MTAP*) [38]. Hedan *et al.* [86] also identified several private CNAs unique and recurrent to each breed, perhaps suggesting a difference in initiation and/or progression leading to a more universal HS genomic phenotype once the tumour develops. Molecular work on canine HS continues, and this hopefully will inform our understanding and treatment approaches to human HS.

(iv) Haemangiosarcoma

Angiosarcomas and haemangiosarcomas are an aggressive group of tumours that have been studied extensively in both canines and humans. Initially thought to be of endothelial cell origin [87,88], there is now suggestion that these aggressive sarcomas of blood vessels may be of haematopoietic origin [89–91]. In humans, angiosarcomas are a very rare, heterogeneous subgroup of soft tissue sarcoma, representing much less than 1% of all tumours. These malignant vascular tumours occur spontaneously as primary tumours and also as secondary tumours following radiation therapy or in the context of chronic lymphoedema [92,93]. Almost half of angiosarcomas occur in the head and neck, though these represent less than 0.1% of all head and neck malignancies [94]. Insidious in nature, clinical symptoms of angiosarcomas often do not manifest until the disease is well advanced. In the dog, haemangiosarcomas frequently involve major vascular organs, (spleen, liver, heart), and also can be subcutaneous. As in humans the tumours are indolent and often remain undetected until the point at which the vascular mass ruptures and the dog suffers internal bleeding that can result in death. While haemangiosarcomas can affect any breed, those of notably high risk include the golden retriever, German shepherd, Portuguese water dog and Australian shepherd.

Gorden *et al.* [95] performed genome-wide expression profiling of a small number of primary canine haemangiosarcomas

($N = 6$ golden retrievers, $N = 1$ Rottweiler, $N = 1$ golden retriever × Great Pyrenees, $N = 1$ Portuguese water dog) and determined three distinct haemangiosarcoma subtypes associated with: angiogenesis (group 1), inflammation (group 2) and adipogenesis (group 3) [95]. The authors investigated haemangiosarcoma cell lines and discovered expression of multiple and distinct markers for early endothelial, haematopoietic and myeloid cells along with several phagocytic and adipogenic functional experiments [95], further supporting the multipotent potential and origin of this blood vessel sarcoma. Genome-wide DNA copy number profiling of canine haemangiosarcoma has also been performed using high-resolution oaCGH [96]. In this study, primary intra-abdominal haemangiosarcomas ($N = 75$; golden retriever ($n = 40$), Australian shepherd ($n = 10$), German shepherd ($n = 10$), flat-coated retriever ($n = 9$) and BMD ($n = 6$)) were assessed and the data revealed a relatively low rate of CNAs with small amplitudes. Despite the presence of multiple passenger alterations, potential recurrent driver alternations were seen in CDKN2A, VEGFA and SKI. Interestingly, VEGFA gains were observed at nearly half the rate in golden retrievers compared with the other breeds (22 versus 40%) [96]. These data support an alternative origin of tumorigenesis among breeds and multiple haemangiosarcoma molecular subtypes owing to alternative activating pathways as demonstrated in the gene expression studies. Further work comparing canine haemangiosarcoma to human angiosarcoma is now awaited.

(b) Haematological malignancies

(i) Lymphoma

Haematological malignancies are common forms of cancer in both dogs and humans. In 2014, approximately 71 000 new cases of human NHL were diagnosed in the USA (http://www.cancer.org). In the domestic dog, key opinion leaders estimate that over 250 000 cases of canine lymphoma (comparable to NHL) were diagnosed in the same period. The high degree of similarity between human and canine lymphoma has been extremely helpful in understanding this disease in both species [97–99]. The high similarity in pathologic presentation of canine and human lymphoma allows for use of World Health Organization (WHO) criteria for accurate and reproducible classification of the canine tumours [100,101]. In human NHL, the vast majority (approx. 90%) of cases are of B-cell origin. In the domestic dog, the proportions of B- and T-cell lymphomas across all dogs is estimated to be approximately 2 : 1, but the immunophenotype prevalence in individual breeds is highly variable [102]. A large study of canine lymphoma characterized 608 cases based on cytomorphological, histomorphological and immunological criteria and importantly included both epidemiological and clinical data [103]; the majority of tumours (76%) were classified as high-grade malignant lymphomas, highlighting the clinical importance of understanding both lymphoma risk and designing novel therapeutic approaches. As is the case across all breeds, approximately two-thirds of the canine lymphomas in this cohort were classified as B cell (CD3−, CD79a+) with one-third classified as T-cell lymphomas (CD3+, CD79a−) [103].

Diffuse large B-cell lymphoma (DLBCL) has been one subtype of canine lymphoma that has been very well studied with genomic profiling. Richards et al. used IHC and gene expression profiling on canine DLBCLs ($N = 49$) and identified similar profiles to human DLBCL, including activation of NF-κB pathway genes and immunoglobulin heavy chain alterations [104]. Although some differences with human lymphoma existed (lack of BCL6 and MIM1/IRF4 protein expression), the authors concluded they could identify germinal centre and post-germinal centre subtypes in canine DLBCL, including different survival times, and that their canine findings reflect human DLBCL [104]. Using a bivariate mixture model based on two-species data, Su et al. [105] were also able to use gene expression profiling to distinguish both the germinal centre B-cell-like DLBCL and the activated B-cell-like DLBCL, including different clinical outcomes based on survival. Another study used gene expression profiling on 35 canine lymphoma samples to define three major groups: (i) low-grade T-cell lymphoma, composed entirely by T-zone lymphoma; (ii) high-grade T-cell lymphoma, consisting of lymphoblastic T-cell lymphoma and peripheral T-cell lymphoma not otherwise specified and (iii) B-cell lymphoma, consisting of marginal B-cell lymphoma, diffuse large B-cell lymphoma and Burkitt lymphoma [106]. Similar to the DLBCL studies, the genomic subtypes were associated with different clinical outcomes. Remarkably, the authors distilled their gene expression profiling into four genes whose expression could reliably predict lymphoma subtype and survival (CD28, ABCA5, CCDC3 and SMOC2) [106]. These findings now need to be confirmed in larger studies in human lymphomas to assess their universal clinical utility.

(ii) Leukaemia

Leukaemia is another haematological malignancy with shared high incidence in dogs and humans. Genomic studies in canine leukaemia are underway, although recent results display similar mechanisms driving leukaemogenesis. RB1 deletions in chronic lymphocytic leukaemia and BCR−ABL fusion in chronic myeloid leukaemia (CML) were among the first cytogenetic aberrations detected in canine cancers that mirror the corresponding human cancers [107]. The BCR−ABL tyrosine kinase translocation (the so-called 'Raleigh chromosome' in dogs and 'Philadelphia chromosome' in humans) has since been demonstrated to be present in additional subtypes [108,109] and proven useful for monitoring cytogenetic remission in CMLs [110]. Another canine study included acute lymphoblastic leukaemia (ALL)/acute undifferentiated leukaemia (AUL) ($N = 11$) and chronic lymphocytic leukaemia (CLL) ($N = 12$) and demonstrated increased c-KIT expression in the ALL/AUL samples [111], offering the possibility of using tyrosine kinase inhibitors as a treatment option in canine leukaemia, an approach similar to that used for human leukaemia with tyrosine kinase-affected pathways.

(c) Bladder cancer

Bladder cancer, also called transitional cell carcinoma (TCC), or urothelial carcinoma (UC) is yet another tumour that affects both humans and their pet dogs [112,113]. In humans, environmental exposure, including tobacco smoke, is a major risk factor for UC. In dogs, however, the risk for UC appears to be mostly genetic through predisposition [13]. Similar to osteosarcoma, the molecular genetics/genomics of canine UC reflect human UC, and the knowledge gained through canine therapeutic trials in UC benefits both dogs and humans [114]. A recent study explored aCGH in canine UC ($N = 31$), compared canine data with comparable results in human TCC ($N = 285$)

and discovered both large chromosomal and focal regions of alterations shared between the species even among a large amount of background genomic instability [18]. Given the strong environmental risk for UC in humans and the prominent genetic risk in dogs, the study of shared genomic events leading to UC tumorigenesis will prove important for both prevention and treatment across species. The introduction of sea lion genomic data for sea lion specific UC will further hone candidate genes for clinical targeting (see §4).

(d) Intracranial malignancies

The clinical and histological presentation of intracranial malignancies affecting human and dog are highly comparable, allowing similar diagnostic criteria to be used from both species [115,116]. In support of the role of the pet dog as a model for such cancers, canine and human intracranial tumours share key histopathological features that are absent in rodent models [117]. There is considerable potential to exploit the dog as a preclinical model for development and evaluation of novel brain tumour therapies [118]. It is widely accepted that short-nosed (brachycephalic) breeds, such as boxer, pug and bulldog, are predisposed to gliomas [7,119,120], while longer nosed (dolichocephalic) breeds, such a collies, golden retriever and Labrador retriever, are more predisposed to meningiomas [11].

(i) Meningioma

While meningiomas represent approximately 25% of adult primary intracranial tumours in human patients [116], they are estimated to comprise almost 40% of all canine intracranial neoplasms [121,122], which largely reflect the enormous popularity of several medium/long-nosed dog breeds. The elevated incidence of meningiomas in the dog, as compared to human populations is of particular concern in veterinary medicine and simultaneously offers a higher caseload to investigate meningioma biology. Meningiomas in both species are highly comparable and share similar phenotypes and gene expression profiles [116,121,123]. Genomic profiling of canine meningiomas for DNA copy number by Thomas et al. [11] indicated that canine meningiomas share a limited extent of whole chromosome aneuploidy with their human counterpart. Importantly, the authors hypothesized that by considering the DNA copy number data from both species, the shared aberrations should be the focus of research; for example, in this study they were able to reduce the size of conserved genomic segments by as much as 50-fold. Interrogation of the minimally shared regions revealed genes of interest that are now being investigated for their functional significance in meningioma biology.

(ii) Glioma

Intracranial gliomas are the most common and lethal primary brain tumours in both the human and canine populations. These tumours are particularly detrimental to the paediatric age group, accounting for 80% of malignant brain tumours in children less than 18 years old. In human adults, gliomas progress from low-grade (I–II) tumours to high-grade (III–IV) tumours and are often rapidly fatal once detected, with long-term survival in grade IV glioblastoma multiforme (GBM) averaging less than 1 year [124]. The molecular genetics of human GBMs have been studied in depth [125,126], with three main pathways identified as RTK/RAS/PI-3K, p53 and

RB signalling [125]. Human patients often present with neurological symptoms such as headaches and seizures, and despite the vast amount of genomic data and novel therapies now available, GBMs recur quickly and aggressively after resection and often lead to death [124]. Several of the human cancer predisposition syndromes include gliomas in their clinical spectrum [127–133], supporting the genetic risk for development of these tumours.

Among canines, gliomas are the second most common brain tumour behind meningiomas and occur with the highest frequency in brachycephalic dog breeds [7,119,120]. Published and anecdotal incidences of brain tumours in boxers, mostly gliomas, range from 5 to 25% incidence [119,120], while some individual pedigrees can have even higher presentation rates. Similar to humans, an untreated glioma in a dog will rapidly progress to a stage IV GBM. Previous cytogenomic studies of canine intracranial malignancies by Thomas et al. [11] revealed genomic architecture similar to the human counterparts. Similar to humans, survival in dogs with gliomas is extremely poor despite treatment ranging from chemotherapy, radiation therapy, hyperthermia, to gene and vaccine therapy [134–138]: most dogs (and humans) will present with neurological symptoms such as seizures [139] and unfortunately die within months of diagnosis.

Genomic analyses of human gliomas reveal increasing molecular complexity as the clinical tumour stage progresses, along with accumulation of specific driver mutations [125,126,140]. Our own genomic data demonstrate very distinct patterns of genome-wide instability when measuring CNAs in human GBMs (JD Schiffman 2015, unpublished data). Genomic analysis of canine GBMs reveals a very similar pattern [11]. The comparison of genomic changes in canine versus human GBMs, and early- versus late-stage tumours, will permit the continued identification of drivers versus passenger mutations.

(e) Melanoma

Human melanomas are the most common malignant skin cancers, often occurring in sun-exposed areas due to UV exposure [141,142], although the rarer mucosal melanomas also can occur in people [143–145]. In humans, as described previously (§2), germline mutations in CDKN2A can lead to familial melanoma with presentation at a young age regardless of sun exposure [42]. Dogs also develop melanoma, and similarly to all the other cancers discussed in this review, these melanocytic canine tumours will very closely resemble human melanoma, emphasizing the beneficial role of the canine preclinical model in studying both UV and non-UV pathways in melanoma [20,146]. Furthermore, the dog has been extremely useful for clinical trials and has contributed to a phase I study for DNA vaccination with xenogeneic human tyrosinase for advanced malignant melanoma [147–151]. Poorman et al. [152] used aCGH profiling to compare cutaneous melanomas (often benign) with the more aggressive oral mucosal form. Distinct patterns of CNAs emerged in the malignant tumours including recurrent gains of dog CFA 13 and 17 and loss of CFA 22, whereas the more benign tumours were more copy number neutral, presenting fewer CNAs (except for recurrent gain of CFA 20q15.3–17) [152]; this pattern resembles that reported with human melanoma, where malignant melanoma can be differentiated from benign nevi using genomic microarray based on number of CNAs [153]. Canine mucosal melanomas

display specific and unique 'sigmoidal patterns' of copy number loss followed immediately by a gain on CFA 30q14, a characteristic feature conserved on HSA 15 in human mucosal melanoma [154]. In addition, both species show numerous other CNAs including frequent gain of c-*MYC* and deletion of *CDKN2A* [152]. Other recent studies have shown microRNA (mi)R-203 to be a common tumour-suppressive miRNA in both human and canine melanoma cell experiments [152]. Clearly, the study of canine melanoma, especially mucosal melanoma, offers an opportunity to understand melanoma biology and rapidly translate that information into both veterinary and medical clinical care.

4. Other animals besides dogs (sea lions, whales, bats and naked mole rats)

In addition to canines, many other animals offer their own unique opportunity to better understand the universal processes involved in tumorigenesis. Some of these animals, such as dogs, are more prone to develop cancer, while others seem to be resistant to its development. By studying both ends of the cancer-risk spectrum, it is hoped that the knowledge gleaned will help with both the treatment and prevention of cancer.

For over half a century, marine mammals have been widely accepted as highly suited sentinels for assessing the health of the world's oceans. The typical lifespan of marine mammals is sufficient to allow assessment of the development of numerous chronic diseases, including cancers [155,156]. The number of marine mammals diagnosed with cancers has been increasing over the past 30 years. Of the 500 live adult and sub-adult free-ranging California sea lions (CSLs) that strand on the west coast of the USA each year, 200–300 are admitted to the Marine Mammal Center in Sausalito, California for rehabilitation. Necropsy data indicate that approximately 20% have neoplasms, of which 85% are aggressive, widely metastatic genitourinary carcinomas [157,158]. While the gamma herpes virus, otarine herpesvirus-1 was initially thought to play a key role in urogenital tumour pathogenesis [159,160], this virus has been reported in the genital secretions of healthy sea lions [161], questioning the role of the virus in cancer pathogenesis. Of key concern for all top-trophic predators (including the sea lion) is the bioaccumulation of high levels of persistent fat-soluble organic contaminants (OCs), including PCB and DDT. Accumulation of high concentrations of these and other persistent OCs are known to cause immune suppression, hormonal and metabolic disruption and genotoxicity leading to cancer [162]. Such compounds remain as major contaminants along the west coast of the USA and continue to pose a serious health threat to the CSL and other marine mammals. Assessment of the levels of DDT and PCB in CSLs with and without genitourinary carcinoma revealed that there are statistically higher levels of both of these OCs in the cancer patients [162]. These cancers, which are not a feature of captive bred and maintained CSLs, are progressive and cause slow painful death in wild animals. Initial genomic investigation of these aggressive urothelial neoplasms, as part of the larger ongoing work by the Sea Lion Cancer Consortium has revealed that they share conserved features with both canine and human counterparts (M Breen 2015, personal communication). We propose that a more detailed investigation of shared cancers using this multi-species approach will highlight genes associated with uroethial carcinogenesis in the context of risk related to both genetics and environmental exposure.

On the opposite side of tumour risk, bats may be protected against cancer (although anecdotal, this seems to be a common consensus in the field) [163]. Naked mole rats, another cancer-free rodent, with an impressive 30-year lifespan, have evolved hypersensitivity to cellular contact inhabitation mediated through alternative *INK4a/b* splicing and very high molecular weight hyaluronan [164–166]. Bowhead whales, the longest living mammal with a lifespan of over 200 years and reportedly very low cancer rates, recently were described to harbour genomic alterations associated with cancer, ageing, cell cycle and DNA repair (e.g. *ERCC1* and *PCNA*) [167]. Elephants represent another large mammal that appears to be protected from cancer [168,169], and various studies are underway to explain the molecular basis for this phenomenon known as Peto's paradox (large and long-lived animals that appear to be cancer resistant) [170–175].

The study of comparative oncology truly embraces all cancer risks, great and small, including humans and all types of animals, wild and domesticated. Working in a transdisciplinary setting, colleagues provide expertise across the basic sciences, medical oncology, tumour biology, pharmacology, evolutionary biology, epidemiology, patient care, drug development, clinical trials and a series of other key disciplines. Whether the primary research focus of the individual is to seek benefit for the human or animal patient, the combined goals of the field are to advance our overall understanding of oncology and translate this towards improving the health and welfare of all animals affected by cancer.

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